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Preventing influenza in younger children

S. Esposito, C. Tagliabue, L. Tagliaferri, M. Semino, M. R. Longo and N. Principi

Pediatric Clinic 1, Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

Abstract

Influenza is common in infants and children: attack rates vary from 23% to 48% each year during inter-pandemic periods, and are even higher during pandemics. Severe cases occur more frequently in children with underlying chronic diseases; however, epidemiological studies have clearly shown that influenza also causes an excess of medical examinations, drug prescriptions and hospitalizations in otherwise healthy children (particularly those aged <5 years), as well as a considerable number of paediatric deaths. Childhood influenza also has a number of social and economic consequences. However, many European health authorities are still reluctant to include influenza vaccinations in their national vaccination programmes for healthy children because, among other things, there are doubts concerning their real ability to evoke a protective immune response, especially in children in the first years of life. New hope for the solution of these problems has come from the introduction of vaccines containing more antigens and the possibility of intradermal administration. However, further studies are needed to establish whether universal influenza vaccination in the first years of life should be recommended, and with which vaccine.

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Corresponding author: S. Esposito, Department of Maternal and Pediatric Sciences, Università degli Studi di Milano, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Via Commenda 9, 20122 Milano, Italy
E-mail: susanna.esposito@unimi.it

Introduction

Influenza is common in infants and children: attack rates vary from 23% to 48% each year during inter-pandemic periods, and are even higher during pandemics [1]. Severe cases occur more frequently in children with underlying chronic diseases; however, epidemiological studies have clearly shown that otherwise healthy children (particularly those aged < 5 years) can experience significant clinical problems when infected by influenza viruses. Influenza causes a substantial excess of medical examinations, drug prescriptions and hospitalizations in healthy children, and a number of influenza-related deaths in paediatric subjects without any risk condition [2–6]. Children are the main cause of the spread of influenza in the community because they shed greater amounts of virus for a longer time than adults. This means that they frequently infect their own households and give rise to various clinical, social and economic problems, including parental absenteeism from work [7].

Yearly administration of influenza vaccine to children at risk has been recommended by health authorities worldwide for several years [8,9], but its use in healthy children is widely debated. The most favourable attitude is found in the USA, where healthy children aged 6–23 months have been included in the list of subjects for whom influenza vaccination should be recommended since 2003, and subsequent additions have led to universal vaccination being officially recommended for all subjects aged between 6 months and 18 years since 2008 [10]. This lead has been followed by a number of Asian and Latin American countries although, in most cases, vaccination is suggested only for healthy children in the first years of life. In contrast, despite repeated recommendations by multinational experts and advisory groups [11–13], only six European countries (Austria, Estonia, Slovakia, Latvia, Slovenia and Finland) have included influenza vaccine in the paediatric vaccination schedule (Table 1) [14]. Moreover, although Finland has implemented a fully reimbursed vaccination programme for

TABLE 1. Influenza vaccination recommendations

WHO/Europe
Recommend that member states vaccinate all individuals ≥6 months [1]
EU
Six member states currently recommend paediatric vaccination [2–4]; recommendations vary by country:
6 months to <18 years of age: Austria, Estonia and Slovakia
6–35 months: Finland
6–24 months: Slovenia, Latvia
USA, Canada and PAHO countries
USA: All individuals ≥6 months of age [5]
Canada: Children 6–24 months of age, and encourages all individuals ≥6 months of age to be vaccinated [6]
Currently, 27 PAHO countries and territories recommend paediatric seasonal influenza vaccination [7][a]

PAHO, Pan American Health Organization.
[a]PAHO recommendations vary by country or territory.

healthy children, this is limited to subjects aged 6–35 months [15].

There are two main reasons for the reluctance of many European health authorities to include influenza vaccination in their national vaccination programmes. The first is their widespread conviction that, although very common, influenza in healthy children is always very mild and therefore does not need to be prevented by vaccination. The second is that there are doubts concerning the real ability of the available vaccines to evoke a protective immune response in children, particularly those in the first years of life. Data regarding the total burden of childhood influenza collected over the last 10 years [1–7] indicate that the first assumption is probably wrong, and that influenza in healthy children (particularly the youngest) gives rise to a substantial medical and economic burden that largely justifies prevention. However, it is significantly more difficult to establish whether the available vaccines are effective enough to support their universal use in healthy children, and two recent meta-analyses have reached opposing conclusions [16,17].

As the course of influenza can be worst in children aged <5 years, the main aim of this review is to discuss whether the currently available data concerning the efficacy of influenza vaccines justifies their universal use in healthy children of this age.

Injectable influenza vaccines

Trivalent inactivated vaccines

Trivalent inactivated vaccines (TIVs; split-virus and subunit TIVs) are the only injectable preparations that are licensed for paediatric use throughout the world. Modern TIVs are very different from the monovalent products containing one whole killed virus (mainly type A) that were first prepared more than 40 years ago [18] because they usually contain fractions of three viruses, the most important of which in immunological terms are the haemagglutinin of each. The three viral strains are chosen every year on the basis of WHO indications of the most probable causes of seasonal influenza epidemics.

Throughout the world, TIVs are only licensed for children aged ≥6 months. Moreover, it is recommended that previously unvaccinated children until the age of 9 years in some countries and until the age of 3 years in other countries should be given two TIV doses 1 month apart [8,9]. However, antibody production after TIV administration increases with age: Walter *et al.* [19] studied children aged 6–23 months in two consecutive years, and found that significantly higher proportions of the older subjects achieved seroprotective antibody concentrations or a four-fold increase in geometric mean titres. Nevertheless, the majority of the youngest children had significantly high levels of antibodies against influenza antigens, which suggests that, although the correlate of protection for children has never been established, some protective efficacy is possible in younger subjects [19]. Unfortunately, there are very few data concerning the immunogenicity of TIVs in children <2 years of age and no definite conclusions can yet be drawn.

Evaluating the data from other studies of the efficacy and effectiveness of TIVs in children is more difficult because there are frequent differences in their endpoints (i.e. the prevention of infection or diseases), the methods used to evaluate them (i.e. seroconversion, seroprotection, culture or PCR), and the characteristics of the children themselves. However, when the few comparable studies are considered together, they clearly show that TIVs are efficacious in preventing influenza in children aged >3 years, although the reduction in the number of disease cases is less than that usually reported for other paediatric vaccinations. Using the pooled results of five studies [20–24] of children aged <9 years, Zangwill and Belshe [20] found that the efficacy of TIVs was 63%, which, together with the indirect advantages of preventing paediatric influenza, may justify the universal use of TIVs in healthy children aged >3 years [25].

However, the efficacy of TIVs is significantly less when the viral strains included in the vaccine do not perfectly match those circulating in the community during an epidemic. Heikkinen and Heinonen [26] examined the data collected in ten clinical trials [22,24,27–34] that evaluated the efficacy of TIVs in children aged <5 years using laboratory tests to confirm the diagnosis of influenza, and found that the protection offered by these vaccines strictly related to the degree of matching: when matching was very good, efficacy was always 60% or more (and in some cases higher than 80%); in the case of a poor match, it was always less than 60%, and sometimes near 0% [26]. The best example in this regard is

provided by the 3-year case–control analysis of infants aged 6–23 months carried out by Cochran *et al.* [31]; this found no efficacy during the first two influenza seasons in which the vaccine strains were largely mismatched with the circulating strains, and an efficacy of 59% during the third year when the match was much better. A strict relationship between vaccine match and vaccine efficacy is also acknowledged in adults [35]. As in the case of immunogenicity, there are very few published data relating to children aged <2 years and it is not possible to state whether TIV administration is really beneficial.

The administration of a larger amount of antigens and the use of the intradermal route have both been tried to overcome the problem of younger children's relatively lower immune response to TIVs. An increase in antibody production after the administration of a larger amount of influenza virus antigens has been found in adults [36], and Skowronski *et al.* [37] confirmed this finding in a study of naive infants aged 6–11 months: the administration of two doses of 0.5 mL (instead of the conventional paediatric dose of 0.25 mL recommended for children aged <36 months) evoked significantly higher antibody levels against all of the antigens included in the vaccine, hence increasing the probability of protection from infection and disease. Although there was no increase in the incidence of adverse events in the children receiving the double dose, further studies are needed to confirm its immunogenicity, safety and tolerability before it can be included in the vaccination schedule of young infants.

The intradermal administration of TIVs has led to interesting results in the elderly, but paediatric data are limited to one study of already primed children aged >3 years in whom this route of administration evoked a protective immune response [38]. However, the lack of data regarding children aged <2 years does not allow the suggestion of this form of administration as a means to overcoming the lower immunogenicity of TIVs.

It can therefore be concluded that administering TIVs may be beneficial in some young children, although the level of protection may be slightly lower than that observed in older subjects. However, as conclusive data are available only for children aged >2 years, nothing can be said about younger subjects. The attempts to increase the immune response and protection by using adjuvants, more antigens and a different route of administration deserve consideration but still need further documentation.

Adjuvanted TIVs

The goal of vaccination is to generate a strong immune response to the administered antigen, one that is able to provide long-term protection against an infection. To achieve this objective with vaccines based on insufficiently immunogenic antigens, it is usually necessary to add an adjuvant. Adjuvant is a term derived from the Latin word *adjuvare*, which means to aid or to help and it was first coined by Ramon in 1926 [18]. It has been shown that virosomes and oil-in-water emulsions can increase the immune response to antigens.

Virosome-adjuvanted vaccine. Virosome-adjuvanted vaccine (VAV) is the only adjuvanted influenza vaccine licensed for use in children in some European countries, but it is not registered in the USA. Virosomes consist of phospholipids that spontaneously form virus-like vesicles to which the influenza virus surface glycoproteins neuraminidase and haemagglutinin are anchored [39], so allowing the development of a compound that is structurally similar to the native virus.

In comparison with conventional TIVs, VAV leads to closer interactions with B lymphocytes and antigen-presenting cells, a stronger T helper 1 response, and greater immune stimulation. The immunogenicity of VAV in humans has been demonstrated in a number of studies of adults and healthy children of any age, but the data regarding younger subjects are limited to a single study in which Kanra *et al.* [40] administered VAV or conventional split TIV to children aged 6–71 months (with a considerable number of children younger than 36 months) and found that the former was slightly more immunogenic. The rates of seroprotection against A/H3N2, A/H1N1 and B influenza viruses were, respectively, 87.8%, 80.1% and 90.4% in the children receiving VAV, and 82.9%, 78.2% and 89.4% in those treated with TIV [40]. The authors also found that the rate of seroprotection against A/H3N2 in unprimed children was significantly higher after VAV (88.8% vs. 78.3%; p 0.03) [40].

The good immune response evoked by VAV was confirmed by data collected by our group in a study of unprimed healthy children aged 6–35 months [41]. The official recommendations state that two half-doses 1 month apart are needed to obtain protection in previously unvaccinated children of this age but, as compliance with this regimen is poor and leaves a considerable number of children unprotected, we evaluated a single dose containing all of the antigen usually administered with the two doses (i.e. 15 μg of each). The results showed that this was as immunogenic as the traditional two doses, suggesting that it improves the stimulation of the immune system [41].

The published data clearly suggest that VAV can evoke a substantial and protective immune response in children aged 6–35 months, but efficacy studies have only included subjects aged >2 years. The available data show that VAV is 84.4% effective in preventing laboratory confirmed influenza A in children aged 3–14 years [42]. We have studied children

aged 2–5 years, and found that VAV is associated with a significantly lower incidence of upper and lower respiratory tract infections, febrile respiratory illnesses, drug prescriptions, missed school days and lost parental working days than no vaccination [43].

Although very few, all of these findings indicate that VAV is a reasonable alternative to TIVs in children aged >2 years, but further studies are needed to establish its immunogenicity and efficacy in children aged <2 years. The data are still too scanty to support its universal use.

Oil-in-water vaccines. Oil-in-water emulsions are simply droplets of oil in water (~100 nm), the most common of which are squalene and tocopherol and tween and lecithin, which can act as adjuvants to increase a vaccine's immunogenicity.

Most of the data regarding oil-in-water adiuvanted vaccines have been collected using the so-called MF59 compound, a squalene-based emulsion that has been widely used since 1997 to increase the immunogenicity of various vaccines including TIV. However, this adjuvant is not currently licensed for use in children, mainly because there are still some unanswered questions concerning its safety and tolerability as it seems to cause transient local solicited reactions more frequently.

Nevertheless, although limited, the data regarding the use of MF59-adjuvanted influenza vaccine (MF59-AV) in patients aged 6–35 months seem to be very promising. Vesikari *et al.* [44] administered two half-doses of MF59-AV or a conventional TIV to unprimed healthy children aged 6–35 months, and found that the haemagglutination inhibiting antibody titres against all of the three vaccine strains were significantly higher after each vaccine dose in the children receiving MF59-AV, who also showed significantly greater cross reactivity against mismatched A strains. Moreover, in a second study, the same authors showed that MF59-AV administered to children under 36 months of age confers longer protection than conventional TIV and, when given as a booster to subjects primed with the same vaccine, evokes a greater immune response [45]. Finally, they have also shown that MF59-AV is significantly more effective in children aged 6–35 months, with absolute vaccine efficacy rates against all influenza strains (94 of 110 cases were the result of vaccine-matched H3N2 viruses) of 86% (95% CI 74–93) for the MF59-AV and 43% (95% CI 15–61) for the vaccine without the adjuvant (TIV); the relative vaccine efficacy rate for MF59-AV versus TIV was 75% (95% CI 55–87). The efficacy rates for MF59-AV were 79% (95% CI 55–90) in children aged from 6 to <36 months and 92% (95% CI 77–97) in those aged from 36 to <72 months of age, compared with 40% (95% CI −6 to 66) and 45% (95% CI 6–68), respectively, for TIV [46].

The immunogenicity induced by the presence of MF59 in influenza vaccines administered to children aged <2 years is further supported by data collected by our group in a study of prematurely born children aged 6–23 months who received the monovalent MF59-AV specifically prepared for the recent A/H1N1/2009 pandemic [47]. Although unprimed, the children seroconverted and remained seroprotected even after a single administration of a reduced dose of the antigen contained in the vaccine, which introduces the idea of spare antigen. Although the pandemic antigen was very strong and the immunogenicity data relating to a pandemic vaccine cannot be compared with those relating to a seasonal vaccine, this finding suggests that MF59 plays a significant role in favouring an optimal immune response; however, further data on the possible future appearance of rare but severe clinical conditions (including narcolepsy and other neurological and autoimmune disorders) are required.

The second oil-in-water adjuvant (the so-called AS03 preparation) is conceptually similar to MF59, but the data regarding its use in children are limited to the pandemic vaccine, and there are no published data concerning its addition to seasonal TIVs. Studies have shown that the AS03-adjuvanted vaccine evokes a protective immune response even in unprimed children aged 6–35 months, although the incidence of adverse events (including high fever) was particularly high, especially in the youngest patients [48]. Moreover, its use in Scandinavia has been associated with a significant increase in the occurrence of narcolepsy, a problem not found in other countries [49].

In conclusion, oil-in-water-adjuvanted vaccines seem to be very interesting products because the few data collected in children aged <36 months suggest that they induce a significantly greater and broader immune response in children at the highest risk of influenza-related complications who have the lowest immune response to conventional TIVs. However, before they can be considered a real means of improving the efficacy of influenza vaccines in younger patients, further studies are needed and, in particular, more data are required concerning the safety and tolerability of AS03.

Live attenuated influenza vaccine

Nasally administered live attenuated influenza vaccine (LAIV) contains cold-adapted, temperature-sensitive, attenuated influenza viruses. It induces a stronger response than TIVs because it mimics natural influenza infection, evoking both mucosal and systemic immunity (including cellular immune response); it is also more easily accepted by children because it does not require an intramuscular injection. In the USA, it was approved for use in healthy subjects aged 2–49 years in

2003 [50] but, in Europe, it has only been authorized for subjects aged 2–18 years [51]. In both areas, it is not recommended for children aged <2 years, children under the age of 5 years with a history of acute wheezing, children and adults with severe asthma, or patients who take medications that can weaken the immune system [50,51].

The immunogenicity of LAIV has been evaluated in subjects of all ages, including children aged 6–72 months. The most important information coming from the studies of children aged 15–55 months is that LAIV evokes a significantly higher level of systemic antibodies than TIVs, and that a number of subjects (62–89% depending on the viral strain included in the vaccine) develop a significant mucosal IgA response [52–57]. It has also been found that primed children are 4.5 times more likely to develop a mucosal immune response than a systemic antibody response, indicating that the mucosal response facilitated by the cellular immune response induced by LAIV is probably the main reason for the postulated superiority of LAIV [58].

Various studies have measured the efficacy of LAIV against placebo and TIV [52–57]. A meta-analysis of placebo-controlled trials in which the recommended two doses of LAIV were administered to unprimed healthy children aged 6–71 months found an estimated efficacy of 77% for antigenically similar subtypes of all three vaccine strains in the vaccine, and 72% for all subtypes regardless of antigenic similarity [58]. A separate analysis of the children aged <36 months showed that age did not significantly affect efficacy, which was 74% for antigenically similar subtypes and 69% for all strains [58]. Moreover, the immune response induced by LAIV was maintained over time: 1 year after having received the first two-dose vaccination 87% of the children were protected against antigenically similar subtypes and 76% against all the circulating subtypes [58].

The studies carried out by Belshe *et al.* [59] provide the best evaluation of LAIV efficacy in children aged <2 years. They monitored the efficacy of LAIV and TIV against culture-confirmed influenza in subjects aged 6–59 months (50% of whom were 6–23 months old), and found 54.9% fewer cases of disease in the group receiving LAIV [59]. The efficacy of LAIV was almost 90% against A/H1N1 and 80% against A/H3N2 influenza viruses, whereas there was no significant difference in the efficacy of the two vaccines against B virus [59]. Furthermore, unlike TIV, LAIV was also effective against poorly matching variants of the A/H3N2 virus [59].

Unfortunately, the good immunogenicity and efficacy of LAIV in younger children was associated with an increased risk of wheezing in the youngest. Wheezing was observed within 42 days of vaccination in 3.8% of the children aged <2 years, but in only 2.1% of those receiving TIV, whereas children ≥2 years could tolerate the vaccine without any risk of bronchospasm [59]. Other studies have not found the same problem [60–62] and have not found the same risk of wheezing, which nevertheless must still be considered as greatly limiting the use of LAIV in infants and young children. Furthermore, the risk of bronchospasm is the main reason why the USA and European health authorities have not licensed LAIV for use in children younger than 2 years or in those who have previously experienced severe obstructive respiratory problems.

Preventing influenza in children aged <6 months

As stated above, none of the available influenza vaccines is recommended for children aged <6 months because their immune response is considered too small to achieve protection, especially during the last trimester of pregnancy. A paper by Glezen's group from the 1980s searched for influenza in children <6 months of age and found maternally transferred antibody, suggesting that in these young infants the immune response postvaccination could be hampered and they could be protected by maternal antibodies [63]. However, as influenza can be dangerous in such subjects, repeated attempts have been made to prevent infection and the consequent disease by immunizing pregnant women. Circulating IgG antibodies and IgA antibodies secreted in breast milk may protect infants [64,65], and a number of studies have shown that up to 6 months of age the children of mothers vaccinated during pregnancy have significantly higher antibody levels than those of unvaccinated mothers [66–68].

The efficacy of vaccination during pregnancy in preventing infantile influenza has been investigated in various studies, which have found reductions in the incidence of influenza disease in the first 6 months of life ranging from 41% to >90% [69–73]. This explains why most experts suggest administering TIV during pregnancy, particularly in the last two trimesters (LAIV must not be used because it is based on live viruses). Unfortunately, compliance with this recommendation is poor in both the USA (where the use of TIV is officially recommended) [73,74] and Europe (where only a limited number of countries include pregnant women among the subjects for whom influenza vaccine is strongly recommended) [73,75].

Conclusions

Analysis of the currently available data concerning the impact of influenza on children and the effects of influenza vaccina-

tion suggest that influenza prevention is needed to reduce disease-related medical, social and economic problems. Unfortunately, although prevention by means of vaccines is satisfactory in older children, it is not the case in those aged <2 years, in whom the immunogenicity of conventional TIVs seems to be reduced. For this reason, and the fact that their efficacy has rarely been evaluated in randomized, placebo-controlled and blinded studies, no firm conclusions can be drawn concerning their possible use in children younger than 2 years. Among the adjuvanted TIVs, VAV has been poorly investigated in children aged <2 years and, despite their greater immunogenicity, oil-in-water adjuvanted TIVs have not yet been licensed because of the lack of adequate safety and tolerability data. It was initially thought that LAIV might provide the best solution, but the emergence of post-administration respiratory problems does not allow its use in children aged <2 years, who are at higher risk of influenza-related complications. Consequently, the possibility of preventing influenza in children aged 6–23 months by means of the currently available vaccines still remains an open question. Administering a TIV containing more antigens or using the intradermal route offer new hope that a definite solution can be found, but further studies are needed to define whether universal influenza vaccination in the first years of life should really be recommended, and with which vaccine. In the meantime, cocooning strategy around the most vulnerable infants (i.e. those with risk factors for complicated disease) should be implemented everywhere and the public health issue represented by influenza in children should be adequately considered at least on a European level.

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Conflicts of interest

The authors have no conflict of interest to declare.

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